

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listing of claims in the application.

1. (Currently Amended) A modified plasminogen activator inhibitor type-1 ("PAI-1") molecule ~~comprising a helix D region, an A3 strand, an A4 strand and an A5 strand, said molecule~~ comprising the amino acid sequence which is at least 95% identical to SEQ ID NO:2, in which one or more amino acid residues are each substituted by wherein SEQ ID NO:2 is modified with a substitution of an amino acid residue that contains a sulphydryl group, such that one or more disulfide bridges are formed ~~between or within said helix D region, A3 strand, A4 strand and/or A5 strand at a position selected from the group consisting of between 10-40, 70-120, 150-220, 300-342, 343-350, 351-400,~~ and wherein said modified PAI-1 molecule has an *in vivo* half-life that is longer than the *in vivo* half-life of a corresponding wild-type PAI-1 molecule, wherein said modified PAI-1 molecule inhibits urokinase plasminogen activator.

2. (Previously Presented) The modified PAI-1 molecule of claim 1 which has an *in vivo* half-life of over 3 hours, 6 hours, 10 hours, 20 hours, 50 hours, 60 hours, 70 hours, 90 hours, 100 hours, 150 hours, 200 hours, 10 days, 12 days, 16 days, 30 days, or 60 days.

3. (Canceled)

4. (Original) The modified PAI-1 molecule of claim 1 wherein said residue that contains a sulphydryl group is cysteine.

5. (Currently Amended) A modified plasminogen activator inhibitor type-1 ("PAI-1") molecule comprising the amino acid sequence of SEQ ID NO:2, wherein ~~4-6~~ one or more amino acid residues of SEQ ID NO:2 is ~~modified with a substitution of substituted by~~ an amino acid residue that contains a sulphydryl group at positions 31, 97, 192, 197, 347, and 355, said modified PAI-1 molecule has an *in vivo* half-life that is longer than the *in vivo* half-life of a corresponding wild-type PAI-1 molecule.

6. (Currently Amended) A modified plasminogen activator inhibitor type-1 ("PAI-1") molecule comprising the amino acid sequence of SEQ ID NO:2, wherein ~~SEQ ID NO:2 is modified with a substitution of an~~ one or more amino acid ~~residue residues is substituted by~~ an amino acid residue that contains a sulphydryl group at positions (i) 31 and 97; (ii) 192 and 347; (iii) 197 and 355; (iv) 31, 97, 192, and 347; (v) 31, 97, 197, and 355;

(vi) 192, 197, 347, and 355; or (vii) 31, 97, 192, 197, 347, and 355, and wherein said modified PAI-1 molecule has an *in vivo* half-life that is longer than the *in vivo* half-life of a corresponding wild-type PAI-1 molecule.

7. (Previously Presented) The modified PAI-1 molecule of claim 1 that further comprises one or more amino acid substitutions that are not substitutions with a sulphydryl-containing residue.

8. (Canceled).

9. (Original) The modified PAI-1 molecule of claim 1 wherein said molecule inhibits tissue plasminogen activator.

10. (Original) The modified PAI-1 molecule of claim 1 wherein said molecule augments endogenous PAI-1 function.

11. (Previously Presented) A method of producing a modified plasminogen activator inhibitor type-1 molecule said method comprising:

(a) introducing into a cell a nucleic acid molecule encoding a modified PAI-1 molecule comprising a helix D region, an A3 strand, an A4 strand and an A5 strand, said molecule comprising the amino acid sequence which is at least 95% identical to SEQ ID NO:2, in which one or more amino acid residues are each substituted by ~~wherein SEQ ID NO:2 is modified with a substitution of~~ an amino acid residue that contains a sulphydryl group, such that one or more disulfide bridges are formed ~~between or within said helix D region, A3 strand, A4 strand and/or A5 strand at a position selected from the group consisting of between 10-40, 70-120, 150-220, 300-342, 343-350, 351-400, and a combination thereof,~~ and wherein said modified PAI-1 molecule has an *in vivo* half-life that is longer than the *in vivo* half-life of a corresponding wild-type PAI-1 molecule wherein said modified PAI-1 molecule inhibits urokinase plasminogen activator; and

(b) culturing the cell under conditions suitable for expression of the modified PAI-1 molecule.

12. (Currently Amended) A method of producing a modified plasminogen activator inhibitor type-1 ("PAI-1") molecule, said method comprising:

(a) introducing into a cell a nucleic acid molecule encoding a modified PAI-1 molecule, said molecule comprising the amino acid sequence of SEQ ID NO:2, wherein ~~1-6~~

one or more amino acid residues of SEQ ID NO:2 are each ismodified with a substitution of substituted by an amino acid residue that contains a sulphydryl group at positions 31, 97, 192, 197, 347, and 355, wherein said active form of said modified PAI-1 molecule has an *in vivo* half life that is longer than the *in vivo* half-life of a corresponding wild-type PAI-1 molecule; and

(b) culturing the cell under conditions suitable for expression of the modified PAI-1 molecule.

13. (Currently Amended) A method of producing a modified plasminogen activated activator inhibitor type-1 ("PAI-1") molecule, said method comprising:

(a) introducing into a cell a nucleic acid molecule encoding a modified PAI-1 molecule, said molecule comprising the amino acid sequence of SEQ ID NO:2, wherein SEQ ID NO:2 is modified with a substitution of in which one or more amino acid residues are each substituted by an amino acid residue that contains a sulphydryl group at positions (i) 31 and 97; (ii) 192 and 347; (iii) 197 and 355; (iv) 31, 97, 192, and 347; (v) 31, 97, 197, and 355; (vi) 192, 197, 347, and 355; or (vii) 31, 97, 192, 197, 347, and 355, and wherein said modified PAI-1 molecule has an *in vivo* half life that is longer than the *in vivo* half-life of a corresponding wild-type PAI-1 molecule; and

(b) culturing the cell under conditions suitable for expression of the modified PAI-1 molecule.

14. (Previously Presented) A method of treating aberrant angiogenesis in a subject in need thereof, said method comprising administering to a subject in which such treatment is desired an effective amount of the modified PAI-1 molecule of claim 1.

15. (Rejoinder) A method of treating cancer in a subject suffering therefrom, said method comprising administering to a subject in which such treatment is desired an effective amount of the modified PAI-1 molecule of claim 1.

16. (Rejoinder) The method of claim 15 wherein said cancer is selected from the group consisting of breast cancer, colon cancer, ovarian cancer, lung cancer, prostate cancer, melanoma, leukemia, lung cancer, skin cancer, pancreatic cancer, bladder cancer, sarcoma, and uterine cancer.

17. (Canceled).

18. (Canceled).

19. (Canceled)

20. (Canceled).

21. (Rejoinder) A method of treating uPA-mediated fibrinolysis in a subject, said method comprising administering to a subject in which such treatment is desired an effective amount of the modified PAI-1 molecule of claim 1.

22. (Rejoinder) A method of treating tPA mediated fibrinolysis in a subject, said method comprising administering to a subject in which such treatment is desired an effective amount of the modified PAI-1 molecule of claim 1.

23. (Original) A pharmaceutical composition comprising a therapeutically effective amount of the modified PAI-1 molecule of claim 1; and a pharmaceutically acceptable carrier.

24. (Canceled)

25. (Canceled)

26. (Canceled)

27. (Currently Amended) The modified PAI-1 molecule of claim 1 wherein said disulfide bridges are formed at positions a position selected from the group consisting of between 29-32, 92-107, 180-197, 246-249, 341-353, 353-374, and 381-391 of SEQ ID NO:2.

28. (Canceled)

29. (Previously Presented) A modified PAI-1 molecule comprising the amino acid sequence of SEQ ID NO:2 wherein amino acid residues at positions: (i) 31 and 97; (ii) 192 and 347; (iii) 197 and 355; (iv) 31, 97, 192, and 347; (v) 31, 97, 197, and 355; (vi) 192, 197, 347 and 355; or (vii) 31, 97, 192, 197, 347, and 355, are substituted with amino acid residues that contain a sulphydryl group.

30. (Previously Presented) A method of producing a modified plasminogen activator inhibitor type-1 (“PAI-1”) molecule said method comprising:

(a) introducing into a cell a nucleic acid molecule encoding the modified PAI-1 molecule of claim 28; and

(b) culturing the cell under conditions suitable for expression of the modified PAI-1 molecule.

31. (Previously Presented) A method of producing a modified plasminogen activator inhibitor type-1 ("PAI-1") molecule said method comprising:

(a) introducing into a cell a nucleic acid molecule encoding the modified PAI-1 molecule of claim 29; and

(b) culturing the cell under conditions suitable for expression of the modified PAI-1 molecule.